xenogeneic light chain immunoglobulin locus is human.

109. The transgenic mouse of claim 88 wherein the
xenogeneic light chain immunoglobulin locus is human.

REMARKS

Claims 83-88 and 95-103 remain pending after amendment.
Applicants have amended the claims to more clearly define the
invention and to improve their form.

Applicants request that this amendment be entered and
fully considered by the Examiner. This amendment does not add
any new matter.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 83-97 and 101-103 stand rejected under 35 U.S.C.
§ 112, first paragraph. The Examiner has stated "the
specification, while being enabling for HPRT, does not reasonably
provide enablement for a xenogeneic DNA wherein the DNA is a
human immunoglobulin gene. . . . [T]he specification fails to
disclose actual working examples of transgenes cloned into YACs
wherein the transgene spans the entire human Ig locus and is
capable of undergoing isotype switching." However, applicants
have amended the claims to recite only the human mu chain and
thus eliminating transgenes capable of undergoing isotype
switching. In view of the amended claims, applicants traverse
this rejection. The amendments are discussed more fully below.

Claim 83 is directed to a transgenic mouse having a
modified genome, said modification comprising inactivated
endogenous immunoglobulin heavy chain loci in which all of the J
segment genes from both copies of the immunoglobulin heavy chain

locus are deleted to prevent rearrangement and to prevent
formation of a transcript of a rearranged locus and the
expression of an endogenous immunoglobulin heavy chain from the
inactivated loci. Further, dependent Claim 84 is directed to a
transgenic mouse which additionally comprises an inactivated
endogenous immunoglobulin light chain locus in which all of the J
segment genes from at least one copy an immunoglobulin light
chain locus are deleted to prevent rearrangement and to prevent
formation of a transcript of a rearranged locus and the
expression of an endogenous immunoglobulin light chain from the
inactivated locus. And, dependent Claim 85 is identical to Claim
84 except that all of the J segment genes from both copies of the
immunoglobulin light chain locus are deleted.

Support for the amendment to claim 83 can be found
throughout the specification, for example at page 11, lines 1-16;
page 15, lines 5-15; page 16, lines 17-26 and lines 31-32; page
19, lines 4-7; page 30, line 9 to line 13; Figures 1 and 2; and
claims 2, 3, 11, 16, 19, 21, 22, 23, 40, 47, 50 and 51 as
originally filed.

Support for the amendments to claims 84 and 85 can also
be found throughout the specification, for example at page 11,
lines 1-16 and 17-23; page 15, lines 5-15; page 16, lines 17-26
and lines 31-32; page 30, line 9 to line 13; and claims 2, 3, 11,
16, 19, 21, 22, 23, 40, 47, 50 and 51 as originally filed. In
addition, Example 4, page 47, line 1 though page 54, line 20 is
directed to inactivation of the mouse light chain J region.

Human Heavy Chain Locus

The Examiner contends that the specification did not
disclose a transgene that spans the entire human Ig locus or is

8

capable of undergoing isotype switching. Applicants' amendment, obviates this ground for the rejection. The amended claims 86-88 and claims that depend therefrom now particularly describe the xenogeneic heavy chain DNA. For example, claim 86 is directed a mouse having the inactivated endogenous immunoglobulin heavy-chain locus of claim 83 and a further modification comprising the inclusion of, in said genome, an immunoglobulin locus encoding a xenogeneic light chain or xenogeneic heavy chain or both. The xenogeneic heavy chain DNA of claims 86-88 further comprises a DNA sequence identical to the germline DNA sequence of human chromosome 14 from the D segment genes of the human immunoglobulin heavy chain locus, continuing through the J segment genes and the constant region genes through Cμ of that locus, wherein said DNA sequence does not include a gamma constant region, and wherein said DNA fragment is operably linked to at least one human V segment gene.

The germline DNA sequence of human chromosome 14 used in the present invention is unrearranged and contains the native sequence and spacing as found on the chromosomal DNA.

Support for such amendments is found in Figure 16 which fully describes the DNA segment of the amendment. Additional support can be found in the specification on page 11, line 31-36; Example 6, page 56, line 1 through page 60, line 3; Example 7, page 70, line 36 through page 72, line 32. Accordingly, the rejection under 35 U.S. C. § 112, first paragraph, should be withdrawn.

Support for new claims 104 through 106 is contained throughout the specification as filed, for example, claims 86-88; page 10, lines 27-37; page 11, lines 16-25 and 31-36; Example 6, page 56, line 1 through page 60, line 3; Example 7, page 70, line

36 through page 72, line 32.

Support for new claims 107 through 109 can be found in claims 95-97 and throughout the specification as filed, for example page 6, lines 6-12; page 10, lines 27-37, and page 11, lines 16-25.

Rejections under 35 U.S.C. § 102 and § 103

Claims 83, 85, 89, and 91 stand rejected under 35 U.S.C. 102(e) as being anticipated by U.S.P.N. 5,591,669 to Krimpenfort et al. ("Krimpenfort"). The Examiner further states that claims 84, 86-88, 90, 92-97, and 101-103 stand rejected under 35 U.S.C. § 103(a) as "unpatentable" over "Krimpenfort as applied to claims 83, 85, 89, and 91 above, and further in view of Krimpenfort (U.S.P.N. 5,591,669)."

The Examiner states that "Krimpenfort discloses gene targeting of the J region of endogenous heavy chain immunoglobulin alleles in ES cells and further discloses that the embryonic stem (ES) cells having the inactivated J region endogenous alleles produce mice incapable of producing endogenous (murine) immunoglobulins."

Applicants' cancellation of claims 89, 90-94, 101-103, without prejudice, obviates these rejections as to those claims. In view of the claim amendments, applicants traverse the rejections as to claims 83 and 85 for anticipation and 84, 86-88, 95-97 for obviousness.

Applicants have amended the claims to use language that the Examiner has already found acceptable in claims issued in United States patent number 5,939,598. Therefore, the present claims are patentable over Krimpenfort for the same reasons that the claims were patentable in those cases. Accordingly, the

10

rejections under 35 U.S.C. § 102(e) and § 103 should be withdrawn.

Rejections under 35 U.S.C. § 103

Claims 84, 86-88, 90, 92-97, and 101-103 stand rejected under 35 U.S.C. § 103(a) as "unpatentable" over <u>Krimpenfort</u>, as applied 83, 85, 89, and 91, further in view of Bruggemann ("<u>Bruggemann</u>") and United States patent 5,545,806 (Lonberg *et al.*) ("<u>Lonberg</u>").

The Examiner did not specify which <u>Bruggemann</u> reference was being used to make the rejection other than to specify later in the paragraph that it was published in September 1989. Applicant assumes that the Examiner intends <u>Bruggemann</u> to mean Bruggemann et al., *Proc. Natl. Acad. Sci.*, 86, pp. 6709-6713 (1989).

The Examiner's rejection is directed exclusively to the dependent claims. Once the rejection of the independent claim is obviated by amendment, claims dependent therefrom must be patentable. In view of the amendments discussed above, the invention as presently claimed is patentable over <u>Krimpenfort</u> as acknowledged by the allowance of related claims in United States patent application 08/464,582 and in claims issued in United States patent number 5,939,598. Accordingly, this rejection is obviated.

Additionally, the <u>Bruggemann</u> reference does not disclose a transgene containing <u>only</u> human immunoglobulin sequences. For example, the sequence of the transgene from J through Cmu in <u>Bruggemann</u>'s minilocus is interrupted by the insertion of the mouse mu enhancer. Further, the <u>Bruggemann</u> transgene contains only one authentic human D segment gene.

11

Moreover, the Bruggemann reference does not disclose a transgene that has a germline sequence that is derived from human chromosomal DNA in its native structure and sequence. For example, as mentioned above, the transgene contains a number of sequence interruptions and non-human elements.

Bruggemann instead refers to an approximately 20 kb heavy chain "minilocus" transgene. The immunoglobulin gene segments in Bruggemann's minilocus neither has the native spacing nor the sequence that is present in the human germline DNA. In the minilocus, the distance between gene segments is substantially shortened compared to germline. Further, Bruggemann's minilocus lacks long and potentially important stretches of human sequence, including human regulatory elements, that are present in the germline fragment used in the present invention. One important example of the failure of the Bruggemann transgene to provide human regulatory elements is that the human mu enhancer in the Bruggemann transgene is incomplete (e.g., only the 5' end of the enhancer is included in the transgene). Bruggemann, thus, neither teaches nor suggests the use of a fully human, germline configured transgene or production of a transgenic mouse containing the same.

Finally, Lonberg is not prior art to the amended claims. Lonberg claims an earliest possible priority date of August 29, 1990. The amended claims are entitled to the benefit of the January 12, 1990 filing date of the parent '008 application. Lonberg does not qualify as prior art under any other sub-section of § 102. Accordingly, the § 103 rejection should be withdrawn.

In view of the above, applicants request withdrawal of the rejections and reconsideration and allowance of the amended

12

claims.

                    Respectfully submitted,

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